REMARKS

Applicant Entity Size

Applicant submits herewith a statement of small entity status. The present application has been filed and prosecuted thus far as though the Applicant were a large entity. However, Applicant has confirmed small entity status and the instant fees, as well as future fees, are paid as a small entity.

Amendments to the claims

Claims 1-6, 9-11 and 13-19 are pending. Claims 2 and 10 are cancelled. Claim 1 is amended. Support for the claim amendments can be found throughout the specification and at least in former claims 2 and 14. After entry of this amendment, claims 1, 3-6, 9, 11 and 13-19 remain pending with claims 13-19 withdrawn. No new matter has been added.

Response to the Claim Rejection under 35 USC Section 112

The Applicant has taken note of the Examiner's rejection of claim 10 as being indefinite for reciting "molecular weight of at least about 7 kDa". Applicant notes that the Examiner erroneously mentioned claim 11 and that this feature is recited in claim 10. Claim 10 has been cancelled and Applicant submits that the rejection is moot.

Response to the Claim Rejection under 35 USC Section 103(a)

The Applicant has taken note of the Examiner's rejection of claims 1-6 and 9-11 as being unpatentable over MALLON in view of SINGLA and TAN. According to the Examiner, it would have been obvious to one of ordinary skill in the art to carry out the precipitation or salting-out of chitosan using a combination of kosmotropic and chaotropic salts as presently claimed in view of MALLON which teaches that a cationic polymer can be effectively precipitated using such salts, in view of SINGLA which teaches that precipitation of chitosan is possible at high electrolyte concentration in an acidic solution, and further in view of TAN which teaches that chitosan can be produced by salting-out in the presence of sodium, potassium, or ammonium sulphate, or sodium, potassium or magnesium chloride.

However, the Applicant respectfully disagrees with the Examiner in this regard.

Moreover, the Applicant disagrees with the Examiner's position that MALLON encompasses a methodology that applies to all cationic water-soluble polymers. The Applicant respectfully submits that this interpretation is erroneous and is an undue extension of MALLON's teaching.

The Applicant is of the opinion that one of ordinary skill in the art would not have considered MALLON to carry out the present invention as claimed, as will be demonstrated herein below. Hence, the skilled person in the art would have not combined the teaching of MALLON with SINGLA and TAN either.

1- The invention

The Examiner is reminded that a key issue of the present invention was to retrieve chitosan (of various molecular sizes) using a method that allowed the retrieved chitosan to be suitable for food consumption and/or biomedical applications. In order to better define the invention, this feature has now been added into claim 1. Obtaining a chitosan having such properties has been rendered possible by the method of the present invention using a combination of kosmotropic and chaotropic salts which are food-compatible or suitable for biomedical applications.

2- Chitosan structure and resulting precipitated salt

Chitosan is a polycationic biopolymer resulting from the presence of a large number of primary amino groups of the ß-*D*-glucosamine (2-amino-2-deoxy-ß-*D*-glucopyranose) building units of chitosan. The number of primary amino groups obviously will vary proportionally with the degree of deacetylation of chitosan. These primary amino groups can exist in an unprotonated or protonated form, depending on pH, as established from basic chemical principles. A method for the manufacturing of chitosan, which is widely used in the industry, as outlined in SINGLA cited by the Examiner is shown in the following scheme.

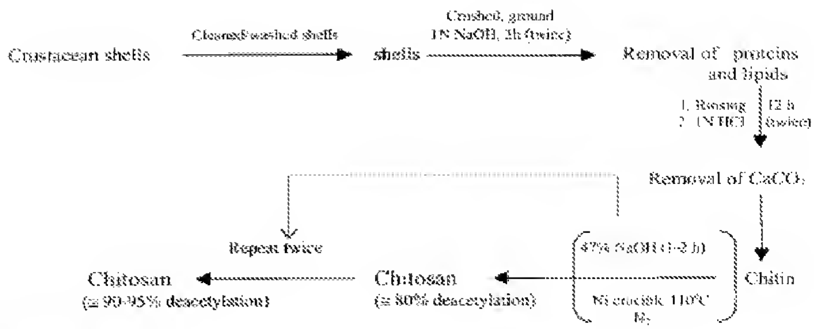
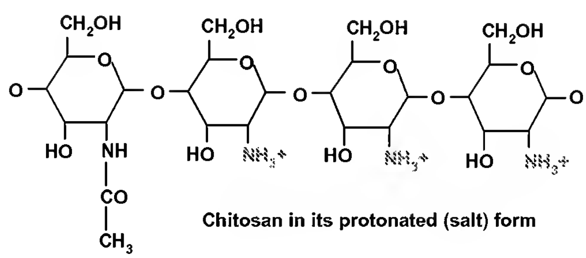


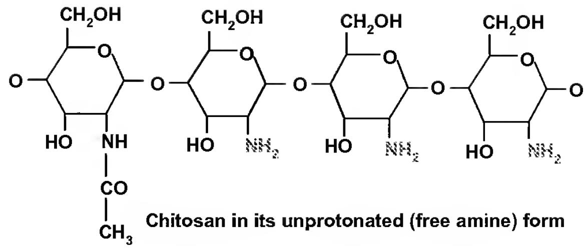
Figure 2 Manufacture of chitosan.

The step of deproteination/delipidation of chitosan with 1N HCl results in a protonated form of chitosan, as depicted by the following schematic structure (structure 1):



Structure 1

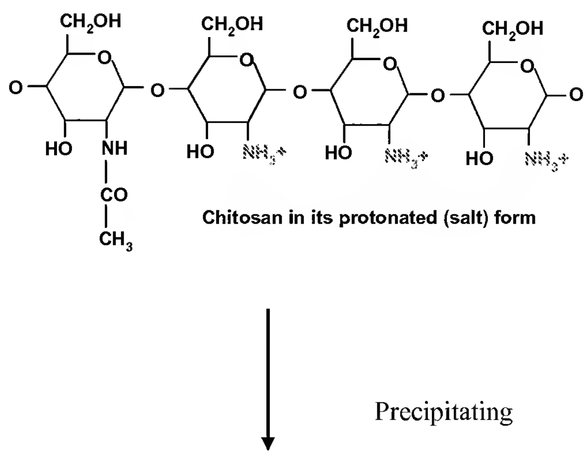
Treatment of chitosan with a hot solution of 47% NaOH for 1-2 h to achieve deacetylation (partially or completely) and chitosan depolymerization (breakdown) results in deprotonation of most if not all primary amino groups of chitosan, yielding the following structure of chitosan (structure 2):



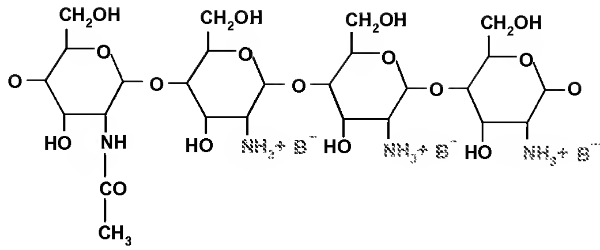
Chitosan in its unprotonated (free amine) form

Structure 2

When chitosan of Structure 2 is dissolved in an acidic solution (as required according to the method of the present invention), it reverts to its protonated (salt) form (Structure 1), which then can function as a week anion exchanger. Then, protonated chitosan is precipitated by addition of any kosmotropic/chaotropic salt of the general structure A^+B^-. An exchange of the counter ion, according to the following equation is observed:



Chitosan in its protonated (salt) form

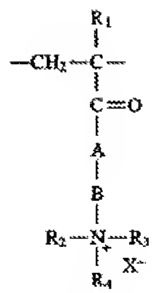


Structure 3

It is worth mentioning that the B^- anion in Structure 3 is not removable by simple washing because of the strength of the ionic bond with the <u>protonated primary amine</u>. Therefore, the nature of the salt used for precipitation is of crucial importance when the salted-out chitosan is to be used for human or animal applications.

3- <u>MALLON</u>

MALLON refers broadly to synthetic cationic polymers and never refers to chitosan or other biopolymers, let alone refers to a process to retrieve a dissolved cationic polymer for human or animal use. In fact, in the more than 50 examples described in the patent, none of these apply to naturally-occurring cationic biopolymers. Furthermore, the structure of the cationic polymers disclosed in MALLON is totally different than the structure of chitosan. MALLON targets synthetic cationic water-soluble polymers possessing a polyamide or polyoxy ether-type backbone and **<u>quaternary</u>, positively charged, amino groups**. Referring for example to claim 3 of MALLON, the polymer structure is as follows:



where R_1 is either hydrogen or CH_3. A is either an oxygen atom or NH. B is an alkylene or oxyalkylene group having 1 to 5 carbons. R_2 and R_3 are each an alkyl group having from 1 to 3 carbons. R_4 is either an alkyl or substituted alkyl group having from 1 to 10 carbons, or an aryl or substituted aryl group having from 6 to 10 carbons, and X is an anionic counterion.

The chemical characteristics of the above polymer of MALLON vastly differ from chitosan which is made of a glucopyranoside backbone substituted in the 2-position of the glucopyranoside with *N*-acetamido or **primary** amino groups. Also, the presence of quaternary amino groups in the polymer of MALLON confers properties that are not comparable to the one of primary amino groups in chitosan. For instance the strength of the ionic bond between the protonated primary amino group and the anionic counterion in chitosan is different than the one between the protonated quaternary amino group and the anionic counterion in the polymer of MALLON. Indeed, quaternary amino groups remain positively charged, even at high pH, as it is known from basic chemistry regarding the properties of amino group-containing compounds. Consequently, the polymer described by MALLON will behave as a cationic polyelectrolyte over the whole range of the pH scale (1 to 14). Therefore, the chemical structure of the polymer described by MALLON cannot provide an obvious clue to the artisan skilled in the art to apply the teaching of MALLON to the retrieval of a chitosan suitable for food consumption and/or biomedical applications. One additional point of consideration is the nature of the backbone of the polymer described by MALLON that differs unmistakably from the polysaccharide backbone of chitosan. The backbone of MALLON's polymer contains recurring units that make up a polyamide or polyoxy ether-type polymer whereas chitosan is made of position-2-substituted glucopyranoside units. It is obvious to any person skilled in the art or to any scientist or engineer that MALLON's polymer and chitosan are polymers of tremendously different

chemical structures. Here again these unmistakably different chemical structures provide additional evidence that the teaching of MALLON cannot create an enabling and obvious source of information for the retrieval of a chitosan suitable for food consumption and/or biomedical applications.

4- SINGLA

In referring to Table 3 and the first full paragraph at page 1049 of SINGLA, the Examiner asserts this document discloses that chitosan is a cationic polymer which is soluble at acidic pH and also that at a high electrolyte concentration salting-out and precipitation of chitosan from the solution is observed.

Applicant has carefully reviewed the paragraph at page 1049 of SINGLA mentioned by the Examiner and is of the opinion that the simple statement that chitosan solubility is inversely related to ionic strength does not give a clue to the person skilled in the art to make use of salts of the Hofmeister's series to retrieve chitosan from aqueous solutions. In this respect, Applicant submits that the publication of SINGLA does not create an obvious source of information with respect to the methodology described and claimed in the present application.

5- TAN

TAN teaches a recipe to prepare chitosan in a high bulk density starting from commercially available chitosan. In essence, the methodology involves dissolving the said material in an aqueous environment by addition of inorganic acids or organic acids. After dissolution is achieved, removal of impurities is performed and chitosan is then brought out of solution by raising pH to values higher than 7 or by salting out, washing the precipitate with water and a combination of water and alcohol, and drying. The inventor claims that a purity of 98.0% to 99.6% is achieved by the process and that a yield of 95% - 99% is obtained. However, Applicant notes that no data are provided to support such high purity and yield. Furthermore, no description of the analytical methods to be used to assess purity is provided either. Hence, the person skilled in the art could not ascertain TAN's statement and methodolody. Furthermore, no data are given to support the applicability of TAN's chitosan to any fields, let alone to human consumption and biomedical applications. In this respect, Applicant submits that the TAN methodology cannot create an enabling and obvious source

of information with respect to the methodology described and claimed in the present application.

6- Conclusion

In view of the above, the Applicant considers that a person skilled in the art would not be led to retrieve chitosan suitable for human consumption or biomedical applications according to the present invention as claimed in view of MALLON. The skilled person would not either consider SINGLA nor TAN. Hence, the skilled person in the art would have not be motivated to combine MALLON with SINGLA and TAN either.

Applicant thus respectfully submits that the presently claimed method is inventive over the cited prior art documents and respectfully requests that the Examiner withdraw this rejection.

Conclusion

Applicant would like to thank the Examiner for his/her time and consideration of this case. If a telephone conversation would help clarify any issues, or help expedite prosecution of this case Applicant invites the Examiner to contact the undersigned at (617) 248-5222. Additionally, please charge any fees that may be required or credit any overpayment to our Deposit Account 03-1721 referencing docket number 2003390-0032.

Respectfully Submitted,
CHOATE, HALL & STEWART LLP

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/JeffreyE.Buchholz/
Jeffrey E. Buchholz
Attorney for Applicant
Registration Number 60,544

PATENT DEPARTMENT
CHOATE, HALL & STEWART LLP
Two International Place
Boston, Massachusetts 02110
Telephone: (617) 248-5000
Facsimile: (617) 502-5002
patentdocket@choate.com